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Processing of Positive Visual Stimuli Before and After Symptoms Provocation in Posttraumatic Stress Disorder – A Functional Magnetic Resonance Imaging Study of Trauma-Affected Male Refugees

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Abstract

Background: Symptoms of anhedonia are often central to posttraumatic stress disorder (PTSD), but it is unclear how anhedonia is affected by processes induced by reliving past traumatic memories.

Methods: Sixty-nine male refugees (PTSD = 38) were interviewed and scanned with functional magnetic resonance imaging while viewing positive, neutral and Scrambled Pictures after being read personalized scripts evoking an emotionally neutral memory and a traumatic memory. We further measured postprovocation state symptoms, physiological measures and PTSD symptoms. We tested whether neural activity associated with positive picture viewing in participants with PTSD was differentially affected by symptom provocation compared to controls.

Results: For the pictures > scrambled contrast (Positive contrast), PTSD participants had significantly less activity than controls in fusiform gyrus, right inferior temporal gyrus and left middle occipital gyrus. The Positive contrast activity in fusiform gyrus scaled negatively with anhedonia symptoms in PTSD participants after controlling for total PTSD severity. Relative to the emotionally Neutral Script, the Trauma Script decreased positive picture viewing activity in posterior cingulate cortex, precuneus and left calcarine gyrus, but there was no difference between PTSD participants and controls.

Conclusions: We found reduced responsiveness of higher visual processing of emotionally positive pictures in PTSD. The significant correlation found between positive picture viewing activity and anhedonia suggests the reduced responsiveness to be due to the severity of anhedonia.

Keywords

posttraumatic stress disorder, functional magnetic resonance imaging, symptom provocation, visual stimuli, emotional numbness, anhedonia

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Introduction

The number of refugees increased to 25.4 million in 2017.¹ Because of the high prevalence of traumatic experiences in this population, 15% to 30% of refugees develop posttraumatic stress disorder (PTSD) and depression.² PTSD is a diagnosis characterized by intrusive thoughts, avoidance, anhedonia, negative mood and cognitive alterations, as well as arousal and reactivity in recall of the psychologically traumatic experience.³ Anhedonia, a central symptom of anhedonia, is reported by 60% of PTSD patients^{4,5} and associated with increased chronicity, suicidality and healthcare expenditures.⁶

The most common approach to studying anhedonia in PTSD has been to present pictures with different valence and arousal and compare neural activity between groups with and without PTSD.⁷ With electroencephalography (EEG), this method has been applied to show that, relative to controls, the vertex positive signals in response to happy faces are smaller in PTSD indicative of reduced early processing.⁸ Similarly, another EEG study showed longer latency P3 components to happy stimuli, suggesting slower processing, in PTSD.⁹ Moreover, functional magnetic resonance imaging (fMRI) studies have found that PTSD is associated with less activity in ventral striatum¹⁰ and increased activity in amygdala¹¹ in response to happy facial expressions.

Despite commonalities, people with PTSD have different emotional reactions in response to traumatic reminders. PTSD patients have been found to respond to symptom provocation with increased physiological arousal¹² and neural activity in the midline retrosplenial cortex and precuneus, indicating increased self-referential processing.¹³ Responding with arousal symptoms is also characterized by increased activity of amygdala and decreased activity in medial anterior brain regions, including medial prefrontal cortex (mPFC).¹⁴ In contrast, other studies have found PTSD patients responding with symptoms of dissociation, feeling disconnected from the body, as if being in a fog.^{3,15} On a neural level, the dissociative response has been found characterized by increased activity in prefrontal cortices and decreased activity in limbic regions such as insula.^{14,15}

The aim of this study was to investigate anhedonia in PTSD using fMRI while presenting positive pictures before and after symptom provocation using personalized Trauma Scripts. We used script-driven imagery of both emotionally neutral and traumatic memories and presented positive, neutral and scrambled visual stimuli. We hypothesized that (1) compared to refugee healthy controls (RHCs), refugees with PTSD would have less activity in the brain's affective network when viewing

positive pictures relative to control pictures, (2) the activity would correlate negatively with symptoms of anhedonia, (3) after symptom provocation, activity related to viewing positive stimuli would be attenuated and more so in refugees with PTSD than in healthy refugees and (4) dissociative and arousal symptoms in response to symptom provocation would correlate with increased activity in mPFC and amygdala activity, respectively. The hypotheses and analysis plan were pre-registered before commencement of data collection.¹⁶

Methods

Participants

Seventy-eight refugees were recruited from May 2016 to April 2018. All participants were male. Another component of the project concerned comparisons of volumetric MR data between refugees and military veterans (mainly males). Since it has also been shown that some brain structures vary with sex,¹⁷ a mixed sex sample would have decreased the statistical power of the volumetric MR study. All participants had Danish, Arabic, Farsi, English or Bosnian as first language, and translators were accessible throughout the period of assessment. Patients with ongoing or previous treatment for PTSD at The Competence Centre for Transcultural Psychiatry (CTP) in Denmark were invited to participate. CTP provides multidisciplinary service to trauma-affected refugees without a primary psychotic or bipolar disorder,¹⁸ and all PTSD participants were enrolled in treatment program consisting of 24 sessions at the CTP which included prolonged exposure therapy.¹⁹ RHCs were recruited via advertisements (public posters and on the internet) or were family or acquaintances of interpreters at CTP. For participants with PTSD, symptoms of depression before the onset of PTSD were an exclusion criterion. Antidepressants were not an exclusion criterion (Table 1), but antipsychotic medication within the last month was. For all participants, alcohol and substance abuse were exclusion criteria, and all participants underwent a substance abuse urine test (Rapid Response, BTNX Inc., Canada) and completed the Alcohol, Smoking and Substance Involvement Screening (Ali et al., 2002).²⁰ Alcohol consumption of less than 21 units per week was permitted. Previous moderate or severe brain injury was exclusion criteria, but previous mild traumatic brain injury (mTBI) was allowed. Traumatic brain injury was identified using Ohio State University Identification Method.²² MRI exclusion criteria included claustrophobia and standard MRI safety incompatibility (e.g. metal implants).

Three participants (one PTSD patient and two RHCs) withdrew consent due to a change of mind, four participants (three PTSD patients and one RHC)

Table 1. Differences between refugees with and without PTSD.

Characteristics	PTSD (n = 38)	RHC (n = 31)	Statistical test and p value
Age, mean years (SD)	45 (11)	38 (12)	$t_{67} = 2.54, p = .011$
Years in Denmark (SD)	15 (10)	15 (10)	$t_{67} = 0.13, p = .901$
Smokers, No. (%)	22 (58)	9 (29)	$\chi^2(1) = 5.74, p = .016$
Years of education, mean (SD), years	13 (5)	16 (3)	$t_{67} = 2.6, p = .011$
Mild traumatic brain injury, ^a No. (%)	21 (82)	23 (74)	$\chi^2(1) = 0.55, p = .459$
Age at first traumatic event, mean years (SD)	18 (9)	17 (9)	$t_{67} = 0.83, p = .405$
Number of different kinds of traumatic events, ^b mean (SD)	9 (3)	4 (3)	$t_{67} = 6.24, p < .001$
Symptoms of arousal (state measure), ^c mean (SD) (range: 0–24)	17.5 (4.3)	8.3 (5.6)	$t_{67} = 7.52, p < .001$
Symptoms of avoidance (state measure), ^c mean (SD) (range: 0–18)	7.8 (6.2)	3.6 (4.2)	$t_{67} = 3.16, p = .002$
Symptoms of dissociation (state measure), ^c mean (SD) (range: 0–18)	7.8 (6.4)	3.5 (4.4)	$t_{67} = 3.13, p = .003$

PTSD: posttraumatic stress disorder; RHC: refugee healthy controls; No.: number of participants.

^aReport of brain or neck trauma following immediately by being dazed, having memory lapse or loss of consciousness for less than 30 minutes.

^bNumber of different kinds of traumatic events that either 'happened to me' or was witnessed as defined by the Life Event Checklist-5.

^cIn response to script-driven imagery of a traumatic memory. Measured with the Response to Script-Driven Imagery²¹ interview. p-values < 0.05 are presented in bold.

opted out of the study due to anxiety during scanning, one PTSD participant was excluded as he later was diagnosed with a primary psychotic disorder and one RHC could not be scanned due to obesity. The clinical and demographical continuous variables of these 9 participants were all within 1 standard deviation from the mean of PTSD and RHC participants who did complete the study. Hence, the study sample for which both clinical and MRI data were available consisted of 38 participants with PTSD and 31 RHCs. The RHC and PTSD participants were matched for country of origin but not for lifetime trauma experience. We also strived to match the two groups for age, but because of limited recruitment possibilities, this was not fully attained.

Clinical Assessment

All participants were interviewed with The Schedules for Clinical Assessment in Neuropsychiatry (SCAN)²³ to diagnose PTSD, depression and enduring personality change after a catastrophic experience. The SCAN was also used to exclude any primary psychotic disorder and manic episodes. All participants with a PTSD diagnosis were further interviewed with the Clinician-Administered PTSD Scale for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (CAPS-5),²⁴ assessed for the past month, and the Life Events Checklist (LEC). All participants were inquired about their trauma, medical, social and smoking history.

The study was approved by the Danish Ethical Committee of Science (H-15006293) and the Danish Data Protection Agency (2012-58-0004). All participants gave written informed consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the Helsinki Declaration of 1975, as

Table 2. Comorbidity, medicine and psychopathology in PTSD participants.

Duration of PTSD, mean years (SD)	14 (10)
Psychiatric comorbidity, No. (%)	33 (87)
Mild depression	7 (18)
Moderate depression	18 (46)
Severe depression	8 (21)
Periodic depression	3 (8)
Enduring personality change after catastrophic experience	14 (39)
Psychotropic medicine, No. (%)	26 (68)
SSRI, No. (%)	12 (32)
Mean mg dose (SD)	104 (44)
SNRI, No. (%)	3 (8)
Mean mg dose (SD)	113 (50)
TeCA, No. (%)	19 (50)
Mean mg dose (SD)	13 (11)
TCA, No. (%)	3 (8)
Mean mg dose (SD)	30 (15)
Clinician-Administered PTSD scale for DSM-5	
Intrusion symptoms, mean (SD)	14.4 (4.1)
Avoidance symptoms, mean (SD)	6.0 (1.8)
Cognition and mood symptoms, mean (SD)	16.1 (5.1)
Arousal and reactivity symptoms, mean (SD)	13.6 (3.5)
Positive and negative symptoms scale	
Positive scale, mean (SD)	11.8 (4.1)
Negative scale, mean (SD)	12.2 (3.2)
General scale, mean (SD)	27 (3.8)

PTSD: posttraumatic stress disorder; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; TeCA: tetracyclic antidepressant; TCA: tricyclic antidepressant; SD: standard deviation; No.: number of participants; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

revised in 2008. Participants were compensated with a fee in addition to earnings during an fMRI task other than that reported here. All expenditures related to public transportation were reimbursed.

Script-Driven Imagery Task Procedures

A week prior to the fMRI session, the first author composed one traumatic (Trauma Script) and one nonemotional script (Neutral Script) of well-remembered past experiences with each participant (for an example see Supplementary Material). Vivid descriptions of ambient and sensory experiences were written in second person singular. The scripts were 30 seconds long, and the procedure was identical to previously published methods.^{25,26} The scripts were read back to the participants, and they then rated their emotional reaction on a scale from 1 to 6, with 6 equalling the participant's worst possible emotional response to a memory. A score of 4 was set as success criteria for the Trauma Script. The scripts were then audio-recorded by either the clinician or the interpreter.

Picture Viewing Task

We selected 96 emotionally positive and 96 emotionally Neutral Pictures from the 'Nencki Affective Picture System'.²⁷ Selection was based on validated ratings of valence²⁷ and absence of culturally offensive contents, which was assessed in collaboration with Iraqi, Syrian and Iranian translators. Ninety-six of the pictures were scrambled for presentation in a control condition (Supplementary Material). The pictures were divided into Set A and B, each with 48 positive, 48 neutral and 48 scrambled images. The content of the nonnoise pictures (i.e. animals, nature, objects, faces) were matched between Set A and B and between the positive and neutral picture category.

fMRI Scanning Procedure

The subjects were placed inside the scanner with headphones, a pulse oximetry probe and a mirror placed on the head coil whereby the participant could watch a screen at the end of the bore. The pulse oximetry probe provided a heart rate measure which we used to examine the impact of the Trauma Script on physiological arousal. A total of four fMRI sessions were then acquired while participants viewed pictures (Figure 1).

Before the first and the second session, the participant listened to the Neutral Script, and before the third and fourth session, they heard the Trauma Script. During the 30 seconds after script reading, participants were asked to recall the experience while paying attention to as many emotional and sensory details as possible. Listening to the script and recalling the experience took place in a silent period with no MRI acquisition. The Trauma Script was always read last to ensure an emotionally neutral state in the Neutral Script sessions.

Picture Set A or B were randomly assigned between subjects to either the first two or last two sessions. The participants viewed blocks of 12 pictures from either the emotionally positive, neutral or scrambled categories. Each block was repeated once with a total of 24 blocks for a total duration of 4 minutes and 48 seconds. The order of the picture condition blocks was random across participants, but the order of blocks in the Neutral Script sessions was repeated in the Trauma Script sessions. Each picture was presented for 1500 milliseconds after which a white cross on a black background was presented for 500 milliseconds. Participants were asked to fixate on the cross in the interval period. Participants' eyes were monitored during the scan with a video camera to ensure commitment to the task.

Immediately after the last scan, the participants were taken out and interviewed about the experience in calm surroundings. The effect of the traumatic script during recall was assessed using the Response to Script-Driven Imagery Scale (RSDI).²⁵ Within a week after scanning, the participants rated the valence of each picture on a 9-point Likert scale (1 = *very negative*, 9 = *very positive*).

Behavioural, Demographic and Physiological Data Analysis

Demographic data and measures of psychopathology were analysed using *t* tests and chi-square tests. Physiological, behavioural and rating data were analysed with a 2 (PTSD and RHC) × 2 (neutral and Trauma Script) mixed model of variance.



Figure 1. Left panel: The participants underwent four cycles of listening to script, recalling the experience and scanning with fMRI while viewing pictures. Right panel: Picture categories (positive, neutral and scramble) were presented in blocks of 12 pictures, each presented for 1500 milliseconds with a 500 milliseconds interval.

fMRI Data Acquisition and Analysis

Data acquisition, radiological assessment and preprocessing are included in the Supplementary Material. Radiological assessment did not lead to exclusion of any participants. For the fMRI data, whole-brain voxel-wise comparisons were made using the statistical parametric mapping (SPM12) software package (<https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>).

At the individual subject level, a general linear model was constructed that modelled one event per stimulus type (positive, neutral and scrambled) plus 24 motion parameters (the 6-parameter affine registration of between functional volumes and their temporal derivatives) as regressors. As we specifically wanted to investigate emotionally positive processing circuits, pictures rated negatively (1–3 on the valence scale) at the subject's postscan valence ratings session were modelled separately and excluded from the positive stimuli regressor. The blood-oxygen level-dependent (BOLD) signal were analysed in a 2 (RHC, PTSD) \times 2 (Neutral Script, traumatic script) \times 3 (positive, neutral, Scrambled Pictures) full factorial random effects model. The primary contrast of interest was the positive > Scramble Contrast (Positive contrast).

A p value threshold of .05 was set as the significance level, and we corrected for multiple comparisons using peak-level family-wise error correction. The MarsBaR tool for SPM (<http://marsbar.sourceforge.net/>) was used to extract parameter estimates (PE) and calculate signal change from baseline in percentage. Correction for nonsphericity was done by restricted maximum likelihood. Unequal variance across script condition and dependence within subjects were assumed. All regressors were convolved with a double-gamma haemodynamic response function. All second level models included age in years, smoking (yes/no) and mTBI as covariates.

Hypothesis Testing

First, we tested if the RHC group had increased activity compared to the PTSD group across script conditions (Hypothesis 1) using a whole-brain voxel-wise t test (RHC > PTSD). To test if the neural activity was negatively correlated with symptoms of anhedonia (Hypothesis 2), we used linear partial correlation coefficients. The correlation coefficients between the mean PE from activated clusters in PTSD participants and anhedonia were tested for significance while controlling for the effect of PTSD severity. As a measure of anhedonia, we used the sum of scores from the three questions in the CAPS-5 that pertain to symptoms of anhedonia (question D5, D6 and D7), and the total CAPS score was used as a measure of PTSD severity. We also ran an exploratory analysis using the total score of subdomain D in

the CAPS as a measure of emotional numbness²⁸ in the same partial correlation analysis. To test if the Trauma Script condition decreased the neural activity relative to the Neutral Script condition across participants, but more so in the PTSD group than in the RHC group, we used two whole-brain voxel-wise t tests (Neutral Script > Trauma Script and Script \times Group interaction) (Hypothesis 3). To test the association between activity in amygdala and mPFC with arousal and dissociation, respectively, (Hypothesis 4), we used the mean PE and postprovocation symptom scores on the RSDI subscales of reexperience and dissociation. We used a neuroanatomical atlas from the automated anatomical labelling (AAL) library in SPM²⁹ to create a region of interest (ROI) volumes of the mPFC (the frontal medial orbital sections) and amygdala bilaterally.

Exploratory Analyses

Two exploratory tests were done. First, we used the neutral > Scramble Contrast to test if any effects found with the positive pictures were specifically associated with positive picture viewing or with picture viewing in general. Next, in a new first-level model, all pictures (except scrambled and pictures rated negatively) were parametrically modelled according to participants' own ratings of the picture's valence. The parametrically modelled regressor was orthogonalized and analysed for group differences (RHC > PTSD). This test allowed us to study if group differences remain when subjective measures of positive valence are taken into consideration.

Results

Demographic Results

Participants were primarily from Syria (29%), Iraq (24%), Afghanistan (20%) and Iran (9%). Yemen, Bosnia, Lebanon, South Sudan, Egypt, Turkey and Jordan were also represented. All participants had experienced at least one event on the LEC. Torture (48%), combat or exposure to a war zone (28%) and witnessing sudden violent death (20%) were most frequently marked as the most traumatic event among PTSD patients. In RHC, it was combat or exposure to a war zone (32%), witnessing sudden violent death (23%) and physical assault (19%). Table 1 presents distribution of sociodemographic variables and traumatic events in all participants and Table 2 presents distribution of comorbidity, medicine and psychopathology in PTSD patients. PTSD participants were significantly older ($p = .001$) and less educated ($p = .001$) than RHC; otherwise, groups did not significantly differ in demography.

Physiological Results

Figure 2 summarizes differences in heart rate during scanning and postscanning rating of the pictures valence. There was a significant main effect of script type ($F(1, 59) = 6.95, p = .011, \eta^2 = 0.105$), a Group \times Script interaction effect ($F(1, 59) = 6.12, p = .016, \eta^2 = 0.093$), but no main effect of group on the mean heart rate ($F(1, 59) = 2.37, p = .129, \eta^2 = 0.039$) (Figure 2). The heart rate for patients went from a mean of 101 ($SD = 13$) to 105 ($SD = 14$) following the Trauma Script, whereas for RHC, it remained mean 98 ($SD = 13$) in both conditions.

Behavioural Results

There was no main effect of script type on the valence ratings of pictures ($F(1, 67) = 0.52, p = .472, \eta^2 = 0.007$) and no Group \times Script interaction effect ($F(1, 67) = 0.32, p = .576, \eta^2 = 0.004$). There was a Group \times Category interaction effect ($F(1, 67) = 5.9, p = .018, \eta^2 = 0.081$) driven by patients rating the positive picture category (mean = 6.3, $SD = 1.2$) less positive than the RHC (mean = 6.9, $SD = 0.9$). [STD has been changed to SD in the sentence “There was a Group \times Category interaction effect. . .” Please check that this is correct or edit as needed.]

We used the RSDI to measure the effect of the Trauma Script on symptoms of arousal, avoidance and dissociation. PTSD participants scored significantly higher than RHC on all three symptoms cluster (see Table 1). A post hoc test showed that scores on the symptom cluster ‘Reexperience’ correlated positively with heart rate during trauma recall ($\rho = 0.41, p = .038$) for PTSD participants but not for RHC ($\rho = 0.17, p = .473$).

Brain Imaging Results

Across all participants, the Positive > Scrambled Pictures contrast (Positive contrast) revealed large regions of significant activity including occipital, temporal and parietal cortex as well as thalamus and limbic regions (eFigure 1 in Supplementary material).

Group Differences in Neural Activity When Viewing Positive Pictures (Hypothesis 1)

In the Positive contrast, RHC had increased activity, relative to PTSD, in right fusiform gyrus (voxels: 6, maximum t score: 5.3, montreal national institute (MNI): 36 –45 –18), left fusiform gyrus (voxels: 2, maximum t score: 4.8, MNI: –33 –63 –18), right inferior temporal gyrus (voxels: 4, maximum t score: 5.1, MNI: 48 –66 –3) and left middle occipital gyrus (voxels: 4, maximum t score: 5.1, MNI: –42 –81 0) (Figure 3 and eTable 1 in Supplementary Material).

Correlation Between Neural Activity When Viewing Positive Pictures and Anhedonia (Hypothesis 2)

The mean PE from all activated clusters from the Positive contrast was negatively correlated with PTSD participants’ score on the CAPS subdomain D (anhedonia), after the effect of total CAPS score had been controlled for ($\rho = -0.51, p = .021$). When instead of the anhedonia score, we used the total score of subdomain D in the CAPS as a measure of emotional numbness, the partial correlation analysis was also statistically significant ($\rho = -0.471, p = 0.003$) (Figure 3).

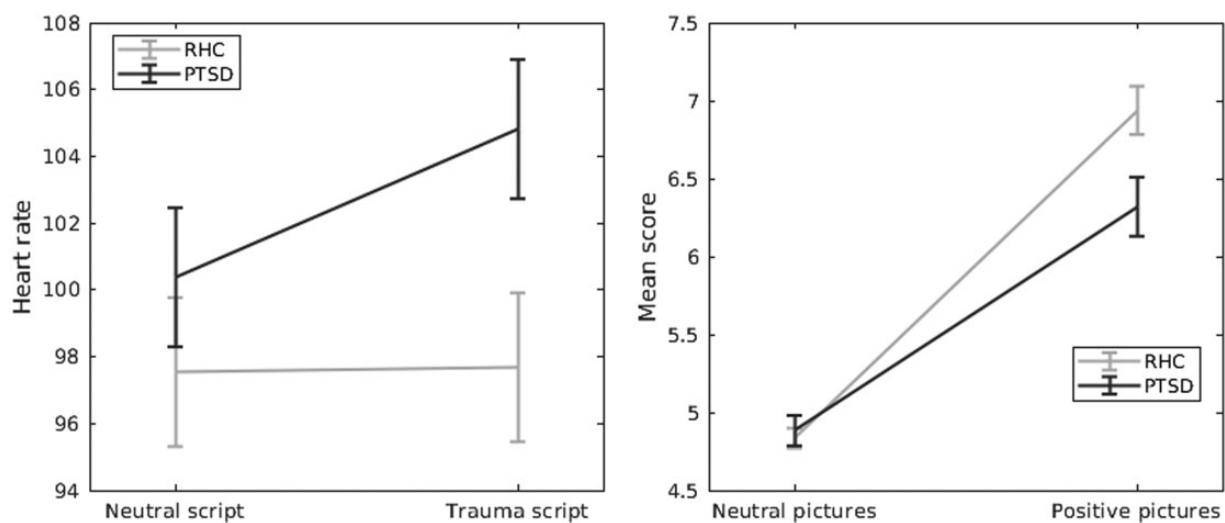


Figure 2. Left panel: The heart rate was affected significantly more by the Trauma Script in patients than in controls. Right panel: Relative to RHC, PTSD participants rated positive pictures significantly less positive. Error bar indicates standard error of the mean (SEM). RHC: refugee healthy controls; PTSD: posttraumatic stress disorder.

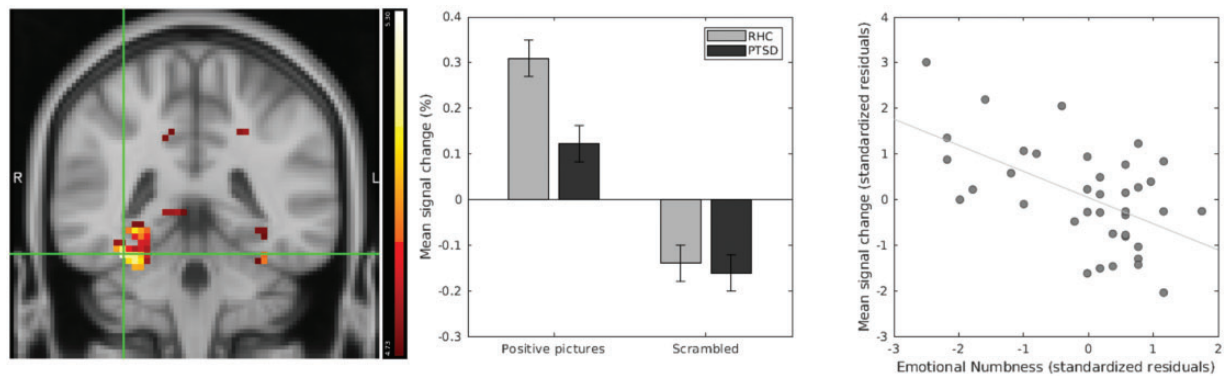


Figure 3. Left panel: Voxels where RHC had more activity than PTSD participants in the positive pictures > noise contrast. Thresholded at $p < .001$, uncorrected and overlaid a standard MNI 2 mm T1 image. After peak-level family-wise error correction, RHC had more activation in both right (crosshair) and left fusiform gyrus, right inferior temporal gyrus and left middle occipital gyrus. Middle panel: Mean parameter estimates across all voxels with more activity in RHC than PTSD. Right panel: Correlation between the parameter estimates from the Positive contrast (after correction) and symptoms of emotional numbness, after having controlled for total PTSD severity. RHC: refugee healthy controls; PTSD: posttraumatic stress disorder.

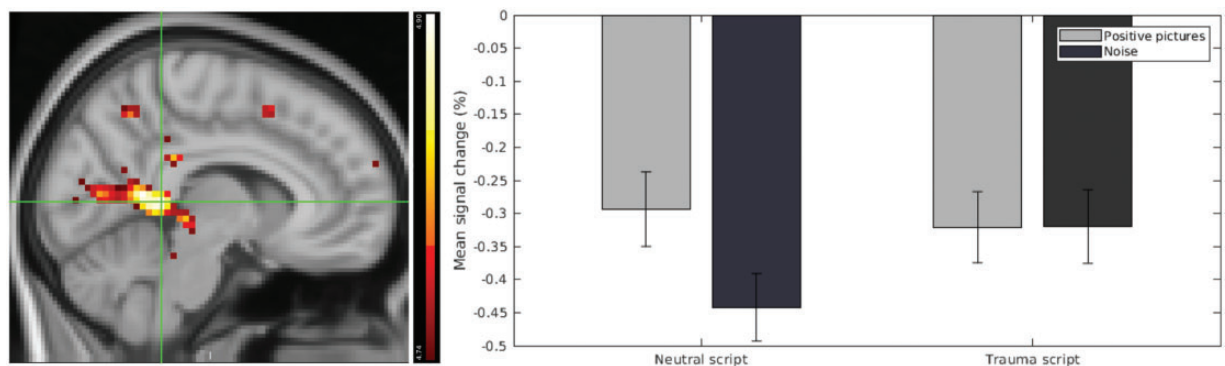


Figure 4. Left panel: Voxels with more activity during the Neutral Script condition compared to the Trauma Script condition in the positive pictures > noise contrast across all participants. Thresholded at $p < .001$, uncorrected and overlaid a standard MNI 2 mm T1 image. After peak-level family-wise error correction, there were script differences in right precuneus, left calcarine gyrus and lingual gyrus. Right panels: The mean parameter estimates from the activated voxels showed that the difference was due to different deactivations of the BOLD signal. The plot displays the average across all three clusters, but in each cluster, the pattern was the same (less deactivation in the noise condition following the Trauma Script).

Effect of Trauma Script on Viewing Positive Pictures (Hypothesis 3)

Next, we tested the effect of the two different scripts on the Positive contrast. The Neutral Script > Trauma Script contrast revealed significant differences in right posterior cingulate gyrus (voxels: 5, maximum t score: 4.90, MNI: 12 -45 3), left calcarine cortex (voxels: 2, maximum t score: 4.74, MNI: -9 -78 9) and right precuneus (voxels: 2, max t score: 4.85, MNI: 9 -51 9) (eTable 1 in Supplementary Material). In these clusters, the Trauma Script resulted in a loss of differentiated signal to positive versus Scrambled Pictures (Figure 4). There was no Script \times Group interaction effect.

Associations Between Symptoms of Reexperience and Dissociation With Neural Activity in Amygdala and mPFC (Hypothesis 4)

There were no associations between scores on the RSDI subscales of reexperience and dissociation and mean PE of the amygdala or mPFC ROIs.

Exploratory Tests

We found no significant voxels in the Neutral Script > Trauma Script contrast using the Neutral Pictures > Scrambled Pictures contrast. When participants' own ratings of the pictures' valence were used in a parametric model of the BOLD signal, we found a

main effect of increased activity across participants in several regions of occipital cortex, fusiform gyrus, lingual gyrus and calcarine gyrus (eFigure 2 in Supplementary Material). However, there was no significant effect of group or script on the activity.

Discussion

We believe this is the first study to investigate the impact of script-driven imagery on the processing of positive visual stimuli in male refugees with PTSD. We recruited refugees as healthy controls, and despite not being matched for traumatic experiences, they all endorsed at least one item from the LEC and, on average, had personally experienced four traumatic life events. Responses on the RSDI subscales suggest that the Trauma Script did cause distress, and change in the heart rate suggest that it affected PTSD participants more than RHC; however, no differences between groups were found in neural processing of the Trauma Script compared to the Neutral Script. Parts of the fusiform gyrus, inferior temporal gyrus and middle occipital gyrus were found to be more activated by the positive pictures in RHC than in PTSD participants, and the signal from these clusters correlated negatively with anhedonia after controlling for total PTSD severity, suggesting that the decreased visual engagement in positive pictures in PTSD is related to anhedonia.

In line with a previous study where PTSD was found to be associated with decreased neural activity in temporopolar regions as well as in left fusiform gyrus relative to healthy controls,³⁰ we found that PTSD participants had decreased activity in visual regions during neural processing of emotionally positive stimuli compared to controls. The middle occipital gyrus forms part of the primary visual cortex where visual information is first processed. The inferior temporal gyrus and fusiform gyrus constitute secondary visual regions where subsequent information processing of socially and emotionally relevant content takes place.^{31,32} Interestingly, the neural activity in both primary and secondary visual cortices in response to a stimulus has been related to the amount of attentional resources allocated to the stimulus and the emotional response it elicits.^{33–36} Meanwhile, the attentional scope has been shown to narrow with increasing signs of negative mood and depressive symptoms.^{37–39} This might explain why the visual encoding was correspondingly weaker in PTSD patients. The importance of the emotional status of the stimulus on the neural encoding can also explain why we did not find group differences in the Neutral Pictures > Scramble Contrast, suggesting that the neural activity differences is specific to positive picture viewing. Moreover, the significant negative correlation

with symptoms of anhedonia supports that the group differences in neural activity are related to PTSD.

We found a difference in neural activity between RHC and PTSD participants when viewing pictures that, based on validation studies in other populations, scored highly positive on a valence scale. When instead we used participants own ratings to model the BOLD response (the parametric model), we no longer found any group differences. Based on this, one might speculate if the difference in neural processing of visual stimuli in PTSD is related to differences in how patients emotionally perceive the stimuli and not dysfunctional neural mechanisms.

Recalling a traumatic memory in both groups affected both precuneus and posterior cingulate cortex which are pivotal regions in the default mode network (DMN)⁴⁰ and previously found to be activated in PTSD following trauma-related stimuli.¹³ The DMN is a set of brain regions proposed to be involved in self-referential thought and mind wandering.^{41,42} The DMN is assumed to switch off whenever attention is directed to external events.^{43,44} The relatively less deactivation during positive picture viewing might reflect a mental state characterized by self-referential thoughts. Interestingly, the effect of the Trauma Script was that the two different stimulus types no longer elicited different neural responses but instead the neural response pattern became uniform between the positive and Scrambled Pictures. While the Trauma Scripts increased the heart rate more in the PTSD group compared to the RHC groups, we did not find brain regions where PTSD participants and RHC differed between the two script types. The Trauma Scripts possibly tapped into acute trauma reactions common across groups rather than the pathophysiological processes of PTSD.

We found no correlation between the effect of script on the Positive > Scrambled Pictures contrast in amygdala and mPFC activity and symptom scores on the RSDI subscales of reexperience and dissociation. One possible explanation is that any potential effect of the Trauma Script on amygdala and mPFC activity might have subsided during the 5 minutes long presentation of stimuli. In that case, the extracted mean PE value would no longer reflect neural activity during postprovocation states of arousal or dissociation. Moreover, since the location for hyperactivity in mPFC during dissociative states in PTSD has shown to vary between studies,¹⁵ we used a mask that covered a large part of mPFC which could have diffused the signal when we averaged across the voxels.

Limitations

One important limitation is that the study included male refugees only. Since gender differences in PTSD

symptomatology have previously been found,⁴⁵ there may also be important gender differences in the neurobiology of PTSD.⁴⁶ Therefore, the results are limited to trauma-affected male refugees. The authors strongly encourage a replication study in females and a general prioritization of mixed-sex or female-only studies so that advances in understanding and potential treatment improvements are not gender-exclusive.

The rating of the pictures was done retrospectively within a week after the scan. Therefore, there is a risk that participants rated the pictures differently from how they were perceived at the time of the scan. In such case, the fMRI model that used participants' own rating to group pictures as positive/neutral would not be accurate.

Also, the study design had an inherent risk of habituation and order effect confounding the script effect (the two scripts were always presented in the same order with the Neutral Script first). However, that there was no script effect on the Neutral > Scramble Contrast suggests that a potential confounding effect of habituation is less likely.

Moreover, antidepressants and depression have each been found to affect neural activity during emotional processing,^{47–49} and the use of antidepressants in our PTSD patients might have attenuated the between-group effect. However, depression in PTSD is present in approximately 66% and can be considered to emerge simultaneously as to two facets of a general post-traumatic psychopathology,^{50,51} and our results can be generalized to a large clinically relevant population with PTSD. Although similar neural activation patterns have previously been found in acute and chronic PTSD during both symptoms provocation^{52–54} and picture viewing,⁵⁵ that PTSD symptoms had been present for 14 years on average limits the results to chronic PTSD. Since we used interpreters, there is a risk of miscommunication though it was not the impression that this has resulted in any clinically relevant information being lost. Our PTSD sample consisted of treatment-seeking male refugees with chronic PTSD and a high trauma load. Although various trauma-affected populations share the PTSD diagnosis, it is becoming increasingly clear that PTSD is a heterogeneous disorder⁵⁶ with corresponding variation in the biological underpinning.⁵⁷ Thus, our results should be interpreted with caution in other PTSD samples than trauma-affected male refugees.

Conclusion

We found decreased neural activity in regions associated with higher visual processing during presentation of positive pictures in PTSD which correlated with anhedonia severity. However, the group difference was absent when the stimuli was modelled according to participants' own valence ratings which suggests a relationship between

behavioural manifestation of anhedonia in PTSD and decreased neural activity in visual regions. We also showed that induced state-related processes like reexperiencing, negative affect induction or dissociation affected PTSD patients to a similar extent as healthy controls.

Author's Note

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Declaration of Conflicting Interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Hartwig R. Siebner has received honoraria as speaker from Novartis Denmark and Sanofi Genzyme, Denmark; has received honoraria as consultant from Sanofi Genzyme, Denmark and has received honoraria as editor from Elsevier Publishers, Amsterdam, The Netherlands and Springer Publishing, Stuttgart, Germany. Hartwig R. Siebner is clinical professor with special focus on precision medicine at the Institute for Clinical Medicine, University of Copenhagen. This professorship is sponsored by Lundbeckfonden (R186-2015-2138).

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Supplemental Material

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